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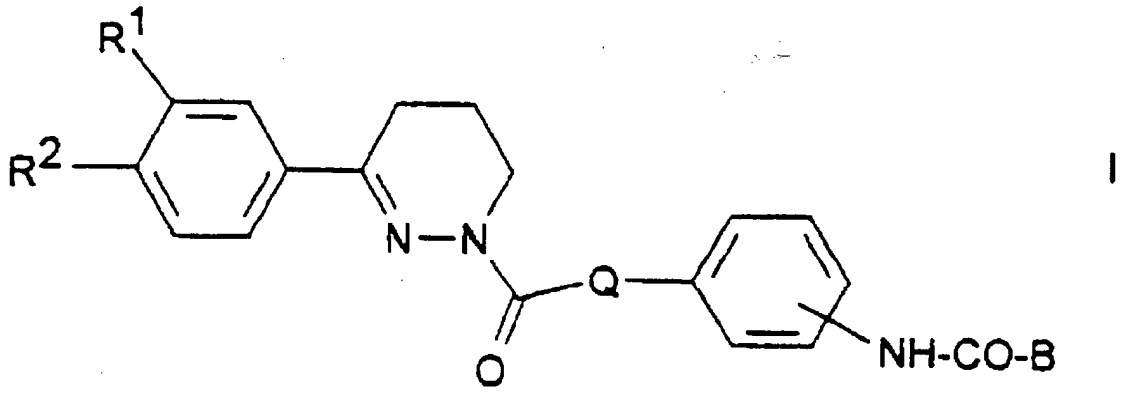
(54) Titre : UTILISATION D'ARYLALCANOYLPYRIDAZINES
(54) Title: USE OF ARYLALKANOYLPYRIDAZINES



I

(57) Abrégé/Abstract:
The invention relates to the use of compounds of formula (I), wherein R^1, R^2, Q and B have the meanings given in claim 1, and/or their physiologically compatible salts for producing a medicament for treating osteoporosis, tumours, arteriosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis and AIDS.

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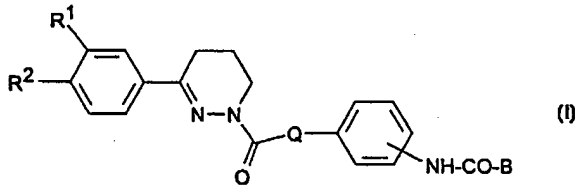
(54) Title: USE OF ARYLALKANOYLPYRIDAZINES

(54) Bezeichnung: VERWENDUNG VON ARYLALKANOYLPYRIDAZINEN



(I)

(57) Abstract

The invention relates to the use of compounds of formula (I), wherein R^1, R^2, Q and B have the meanings given in claim 1, and/or their physiologically compatible salts for producing a medicament for treating osteoporosis, tumours, arteriosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis and AIDS.

(57) Zusammenfassung

Verwendung von Verbindungen der Formel (I), worin R^1, R^2, Q und B die in Anspruch 1 angegebenen Bedeutungen haben, und/oder ihrer physiologisch unbedenklichen Salze zur Herstellung eines Arzneimittels zur Behandlung von Osteoporose, Tumoren, Atherosklerose, rheumatoide Arthritis, multiple Sklerose, Diabetes mellitus, ulzerative Kolitis und AIDS.

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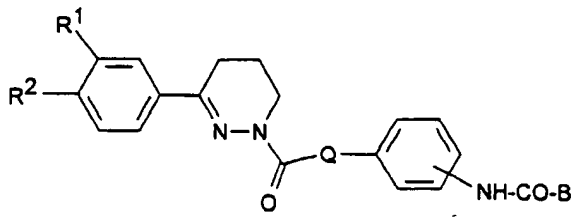
Use of arylalkanoylpyridazines

The invention relates to the use of compounds of the formula I



I

in which

B is A, OA, NH_2, NHA, NAA' or an aromatic heterocycle having 1 to 4 N, O and/or S atoms which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or OA,

Q is absent or is alkylene having 1 to 6 C atoms,

R^1, R^2 each independently of one another are -OH, OR^5, $-S-R^5$, $-SO-R^5$, $-SO_2-R^5$, Hal, $-NO_2$, $-NH_2$, $-NHR^5$ or $-NR^5R^6$,

R^1 and R^2 together are also $-O-CH_2-O-$,

R^5 and R^6 each independently of one another are A, cycloalkyl having 3-7 C atoms, methylene-cycloalkyl having 4-8 C atoms or alkenyl having 2-8 C atoms,

A, A' each independently of one another are alkyl having 1 to 10 C atoms which may be substituted by 1 to 5 F and/or Cl atoms and

Hal is F, Cl, Br or I,

and/or their physiologically acceptable salts for preparing a medicament for the treatment of osteoporosis, tumours, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis and AIDS.

The compounds are known from WO 98/06704.

The invention was based on the object of finding novel uses of the compounds of the formula I, in particular those which may lead to the production of medicaments.

It has been found that the compounds of the formula I and their salts have very useful pharmacological properties together with good tolerability.

In particular, they show a selective inhibition of phosphodiesterase IV, which is accompanied by an intracellular increase of cAMP (N. Sommer et al., Nature Medicine, **1**, 244-248 (1995)).
The inhibition of PDE IV can be demonstrated, for example, analogously to C.W. Davis in Biochim. Biophys. Acta **797**, 354-362 (1984).

The compounds according to the invention can be employed for the treatment of asthmatic disorders. The antiasthmatic action of the PDE IV inhibitors is described, for example, by T.J. Torphy et al., in Thorax, **46**, 512-523 (1991) and can be determined, for example, by the method of T. Olson, Acta allergologica **26**, 438-447 (1971).

Since cAMP inhibits osteoclastic cells and stimulates osteogenic cells (S. Kasugai et al., M681, and K. Miyamoto, M 682, in Abstract of the American Society for Bone and Mineral Research 18th annual meeting, 1996), the compounds according to the invention can be employed for the treatment of osteoporosis.

The compounds moreover show an antagonistic action on the production of TNF (Tumour Necrosis Factor) and are therefore suitable for the treatment of allergic and inflammatory diseases, autoimmune diseases and transplant rejection reactions.
They can be employed for treating memory disturbances, tumours, atherosclerosis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, atopic dermatitis, diabetes mellitus, ulcerative colitis and AIDS.

The action of PDE IV inhibitors in the treatment of asthma, inflammatory disorders, diabetes mellitus, atopic dermatitis, psoriasis, AIDS, tumour growth or tumour metastases is described, for example, in EP 77 92 91.

The anti-inflammatory action of the substances according to the invention and their efficacy for the treatment of, for example, autoimmune disorders, multiple sclerosis or rheumatoid arthritis can be determined analogously to the methods of N. Sommer et al., Nature Medicine, **1**, 244-248 (1995) or L. Sekut et al., Clin. Exp. Immunol., **100**, 126-132 (1995).

The efficacy of PDE IV inhibitors in the treatment of tumours is described, for example, in WO 95 35 281, WO 95 17 399 or WO 96 00 215.

The compounds of the formula I can be employed as pharmaceutically active compounds in human and veterinary medicine. They can furthermore be employed as intermediates for the preparation of further pharmaceutically active compounds.

The compounds of the formula I can have a chiral centre and therefore be present in several stereoisomeric forms. All of these forms (for example R and S forms) and their mixtures (for example the R,S forms) are embraced by the formula I.

The preparation of the compounds is described in WO 98/06704.

A and A' are preferably alkyl, furthermore preferably alkyl which is substituted by 1 to 5 fluorine and/or chlorine atoms.

Alkyl is preferably unbranched and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms, preferably 1, 2, 3, 4 or 5 C atoms, and is preferably methyl, ethyl, trifluoromethyl, pentafluoroethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl or isopentyl.

Cycloalkyl has preferably 3-7 C atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, and further also cycloheptyl.

Methylenecycloalkyl has preferably 4-8 C atoms and is preferably methylenecyclopropyl or methylenecyclobutyl, furthermore preferably methylenecyclopentyl or methylene cyclohexyl, and further also methylene-cycloheptyl.

Alkenyl is preferably vinyl, 1- or 2-propenyl, 1-butenyl, isobutenyl, sec-butenyl, and further preferably 1-pentenyl, isopentenyl or 1-hexenyl.

Alkylene is preferably unbranched and is preferably methylene or ethylene, and further preferably propylene or butylene.

Hal is preferably F, Cl or Br, but also I.

The radicals R^1 and R^2 can be identical or different and are in the 3- or 4-position of the phenyl ring. They are, for example, independently of one another

hydroxyl, $-S-CH_3$, $-SO-CH_3$, $-SO_2CH_2$, F, Cl, Br or I or together methylenedioxy. Particularly preferably, however, they are each methoxy, ethoxy, propoxy, cyclopentoxy, or else fluoro-, difluoro-, trifluoromethoxy, 1-fluoro-, 2-fluoro-, 1,2-difluoro-, 2,2-difluoro-, 1,2,2-trifluoro- or 2,2,2-trifluoroethoxy.

The radical B is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

The radical B is furthermore preferably methyl, ethyl, propyl, n-butyl, methoxy, ethoxy, propoxy, N-methylamino, N,N-dimethylamino, N-ethylamino or N,N-diethylamino.

It is true of the entire invention that all radicals which occur a number of times can be identical or different, i.e. are independent of one another.

Accordingly, the invention provides in particular the use of those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to Ie, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in the formula I, but in which

in Ia R^1 and R^2 are each independently of one another OA,
Q is absent and
B is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, imidazolyl or isoxazolyl;

in Ib R^1 and R^2 are each independently of one another OA,
Q is methylene and
B is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, imidazolyl or isoxazolyl;

in Ic R^1 and R^2 together are $-O-CH_2-O-$,
Q is absent or is alkylene having 1-6 C atoms and
B is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, imidazolyl or isoxazolyl;

in Id R^1 and R^2 are each independently of one another OA,
Q is absent or is alkylene having 1-6 C atoms and
B is A or OA;

in Ie R^1 and R^2 are each independently of one another OA,
Q is absent or is alkylene having 1-6 C atoms,

B is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, imidazolyl, isoxazolyl, A, OA or NH_2.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

In the compounds of the formulae II and IV, R^1, R^2 and Q have the meanings indicated, in particular the preferred meanings indicated.

In the compounds of the formulae III and IV, Q is preferably methylene or ethylene, further preferably propylene or butylene.

B, in the compounds of the formulae III and V, has the preferred meanings indicated, while L is Cl, Br, OH or a reactive esterified OH group.

If L is a reactive esterified OH group, this is preferably alkylsulphonyloxy having 1-6 C atoms (preferably methylsulphonyloxy) or arylsulphonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulphonyloxy, and further also 2-naphthalene-sulphonyloxy).

The starting substances, if desired, can also be formed in situ, such that they are not isolated from the reaction mixture but immediately reacted further to give the compounds of the formula I.

On the other hand, it is possible to carry out the reaction stepwise.

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

The starting substances of the formulae II and III are known in some cases. If they are not known, they can be prepared by methods known per se.

In detail, the reaction of the compounds of the formula II with compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between approximately -20 and approximately 150°, preferably between 20 and 100°.

Suitable inert solvents are, for example, hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles such as acetonitrile; sulphoxides such as dimethyl sulphoxide (DMSO); carbon disulphide; carboxylic acids such as formic acid or acetic acid; nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate or mixtures of the solvents mentioned.

Compounds of the formula I can furthermore be obtained by reacting compounds of the formula IV with compounds of the formula V.

As a rule, the starting compounds of the formulae IV and V are known. If they are not known, they can be prepared by methods known per se.

Thus, the preparation of 1-benzoyltetrahydropyridazine, for example, is described in J. Med. Chem. **38**, 4878 (1995).

In the compounds of formula V, the radical -CO-L is a preactivated carboxylic acid, preferably a carboxylic acid halide.

The reaction of the compounds of the formula IV with compounds of the formula V takes place under the same conditions, as regards the reaction time, temperature and solvent, as is described for the reaction of the compounds of the formula II with compounds of the formula III.

A base of the formula I can be converted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the base and of the acid in an inert solvent such as ethanol and subsequent evaporation. Possible acids for this reaction are in particular those which yield physiologically acceptable salts. Thus, inorganic acids can be used, e.g. sulphuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as ortho-phosphoric acid, sulphamic acid, and furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulphonic or sulphuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic

acid, p-toluenesulphonic acid, naphthalenemono- and -disulphonic acids, and laurylsulphuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, if desired, the free bases of the formula I can also be liberated from their salts with bases (e.g. sodium or potassium hydroxide or sodium or potassium carbonate).

These compounds of the formula I can be used as pharmaceuticals in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, and furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavourings and/or one or more further active compounds, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be employed in the control of diseases in which an increase in the cAMP (cyclic adenosine monophosphate) level leads to inhibition or prevention of inflammation and to muscle relaxation. The compounds according to the invention can be employed, in particular, in the treatment of osteoporosis, tumours, asthma, chronic bronchitis, atopic dermatitis, psoriasis and other skin diseases and autoimmune disorders.

In this connection, as a rule the substances according to the invention are preferably administered in doses of between about 1 and 500 mg, in particular between 5 and 100 mg per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, and on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

Compounds of the formula I can contain one or more asymmetric centres. In this case, they are usually present in racemic form. Racemates that are obtained can be separated into their enantiomers mechanically or chemically, by methods known per se. Preference is given to forming diastereomers from the racemic mixture by reaction with an optically active separating agent.

It is, of course, also possible to obtain optically active compounds of the formula I by methods described above by employing starting substances which are already optically active.

The formula I embraces all stereoisomers and their mixtures, for example the racemates.

Above and below, all temperatures are indicated in °C. In the following examples, "customary working up" means: if necessary, water is added, the mixture is adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10, and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulphate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Mass spectrometry (MS):

EI (electron impact ionization) M^+

FAB (Fast Atom Bombardment) $(M+H)^+$

Example 1

A suspension of 4.70 g of 3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine ("A") in 150 ml of THF is admixed with 2.24 g of potassium tert-butoxide, and the suspension is stirred for 30 minutes. 7.3 g of 4-nicotinoylaminobenzoyl chloride are added, and the mixture is stirred at room temperature for 10 hours. The solvent is removed and the residue is subjected to customary working up. This gives 1-(4-nicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hyrochloride, m.p. 239° (decomposition).

Analogously, reaction of "A"

with 4-isonicotinoylaminobenzoyl chloride gives:

1-(4-isonicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 247° (decomposition)

Example 2

A solution of 2.0 g of 1-(4-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 197° [obtainable by catalytic hydrogenation of 1-(4-nitrobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 203°, in 150 ml of tetrahydrofuran in the presence of 3.5 g of Raney nickel at room temperature] and 1.6 ml of pyridine in 150 ml of acetonitrile is admixed with 1.2 g of nicotinoyl chloride hydrochloride, and the mixture is stirred for two hours. The solvent is removed and the residue is subjected to customary working up. Recrystallization gives 1-(4-nicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 239° (decomposition).

Analogously, reaction of the "amine derivatives" below

1-(3-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 168°;

1-(2-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 154°;

1-(3-aminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 168°;

1-(3-aminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine

1-(4-aminobenzoyl)-3-(3-methoxy-4-methylsulphonyl-phenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

with nicotinoyl chloride gives the compounds below

1-(3-nicotinoylaminobenzoyl)-3-(3,4-dimethoxy-phenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, 159° (decomposition);

1-(2-nicotinoylaminobenzoyl)-3-(3,4-dimethoxy-phenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-nicotinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, 235°;

1-(4-nicotinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 224° (decomposition);

1-(3-nicotinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with isonicotinoyl chloride gives the compounds below

1-(4-isonicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 247° (decomposition);

1-(3-isonicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, 175° (decomposition);

1-(2-isonicotinoylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-isonicotinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 266°;

1-(3-isonicotinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-isonicotinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 244° (decomposition);

1-(3-isonicotinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-isonicotinoylaminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-isonicotinoylaminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine.

1-(4-isonicotinoylaminobenzoyl)-3-(3-trifluoro-methoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-pyridazine

Analogously, reaction of the abovementioned "amine derivatives" with picolinoyl chloride gives the compounds below

1-(4-picolinoylaminobenzoyl)-3-(3,4-dimethoxy-phenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-picolinoylaminobenzoyl)-3-(3,4-dimethoxy-phenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-picolinoylaminobenzoyl)-3-(3,4-dimethoxy-phenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-picolinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-picolinoylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-picolinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-picolinoylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-picolinoylaminobenzoyl)-3-(3,4-methylene-dioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-picolinoylaminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydro-pyridazine,

1-(4-picolinoylaminobenzoyl)-3-(3-trifluoro-methoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-pyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with furan-2-carbonyl chloride gives the compounds below

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(furan-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(furan-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(furan-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(furan-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(furan-2-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with thiophene-2-carbonyl chloride gives the compounds below

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(thiophene-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(thiophene-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(thiophene-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(thiophene-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(thiophene-2-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with pyrazine-2-carbonyl chloride gives the compounds below

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 213°C;

1-(3-(pyrazine-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 204°;

1-(2-(pyrazine-2-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 186°;

1-(3-(pyrazine-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 225°;

1-(3-(pyrazine-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrazine-2-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with imidazole-4-carbonyl chloride gives the compounds below

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(imidazole-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(imidazole-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(imidazole-4-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(imidazole-4-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(imidazole-4-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with 2,4-dimethylthiazole-5-carbonyl chloride gives the compounds below

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(2,4-dimethylthiazole-5-carbonylamino)-benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with isoxazole-5-carbonyl chloride gives the compounds below

1-(4-(isoxazole-5-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(isoxazole-5-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(isoxazole-5-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(isoxazole-5-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(isoxazole-5-carbonylamino)benzoyl)-
3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-
pyridazine,

1-(4-(isoxazole-5-carbonylamino)benzoyl)-
3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-
tetrahydropyridazine,

1-(3-(isoxazole-5-carbonylamino)benzoyl)-
3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-
tetrahydropyridazine,

1-(4-(isoxazole-5-carbonylamino)benzoyl)-
3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydro-
pyridazine,

1-(4-(isoxazole-5-carbonylamino)benzoyl)-
3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-
tetrahydropyridazine,

1-(4-(isoxazole-5-carbonylamino)benzoyl)-
3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-
tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with pyrimidine-2-carbonyl chloride gives the compounds below

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-
3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydro-
pyridazine,

1-(3-(pyrimidine-2-carbonylamino)benzoyl)-
3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydro-
pyridazine,

1-(2-(pyrimidine-2-carbonylamino)benzoyl)-
3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydro-
pyridazine,

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-2-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of the abovementioned "amine derivatives" with pyrimidine-4-carbonyl chloride gives the compounds below

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 196°;

1-(3-(pyrimidine-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-(pyrimidine-4-carbonylamino)benzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-(pyrimidine-4-carbonylamino)benzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl).

Analogously, reaction of

1-(4-aminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-aminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-aminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzylcarbonyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-aminobenzylcarbonyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzylcarbonyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-aminobenzylcarbonyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzylcarbonyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzylcarbonyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzylcarbonyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

with nicotinoyl chloride gives the compounds below

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 225°;

1-(3-nicotinoylaminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-nicotinoylaminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-nicotinoylaminobenzylcarbonyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-nicotinoylaminobenzylcarbonyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-nicotinoylaminobenzylcarbonyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, reaction of 1-(4-aminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine

with isonicotinoyl chloride gives
1-(4-isonicotinoylaminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, hydrochloride, m.p. 209°

and with ethyl chloroformate gives
1-(4-ethoxycarbonylaminobenzylcarbonyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 143°.

Example 3

A solution of 2.0 g of 1-(4-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 197°, and 0.8 ml of pyridine in 160 ml of dichloromethane is admixed with 0.6 ml of ethyl chloroformate ("B"), and the mixture is stirred for two hours. The solvent is removed and the residue is subjected to customary working up. Recrystallization from isopropanol/petroleum ether gives 2.2 g of 1-(4-ethoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 165°.

Analogously, reaction of the "amine derivatives" below

1-(3-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-aminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-aminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-aminobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

with "B" gives

1-(3-ethoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 181°;

1-(2-ethoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-ethoxycarbonylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 147°;

1-(3-ethoxycarbonylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-ethoxycarbonylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 166°;

1-(3-ethoxycarbonylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-ethoxycarbonylaminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-ethoxycarbonylaminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-ethoxycarbonylaminobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, the abovementioned "amine derivatives" and methyl chloroformate give the compounds below

1-(4-methoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 226°;

1-(3-methoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-methoxycarbonylaminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-methoxycarbonylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-methoxycarbonylaminobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-methoxycarbonylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-methoxycarbonylaminobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-methoxycarbonylaminobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-methoxycarbonylaminobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-methoxycarbonylaminobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Analogously, the abovementioned "amine derivatives" and acetyl chloride give the compounds below

1-(4-acetamidobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine, m.p. 230°;

1-(3-acetamidobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(2-acetamidobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-acetamidobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-acetamidobenzoyl)-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-acetamidobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(3-acetamidobenzoyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-acetamidobenzoyl)-3-(3,4-methylenedioxyphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-acetamidobenzoyl)-3-(3-methoxy-4-methylsulphonylphenyl)-1,4,5,6-tetrahydropyridazine,

1-(4-acetamidobenzoyl)-3-(3-trifluoromethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine.

Example 4

A solution of 2.0 g of 1-(4-aminobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine and 0.8 ml of N-ethyl isocyanate in 160 ml of dichloromethane is stirred at room temperature for two hours.

The solvent is removed and the residue is subjected to customary working up. Recrystallization from isopropanol/petroleum ether gives 2.1 g of 1-(4-ethylureidobenzoyl)-3-(3,4-dimethoxyphenyl)-1,4,5,6-tetrahydropyridazine.

The following examples relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2 N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution of 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Analogously to Example E, tablets are pressed which are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

Example G: Capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

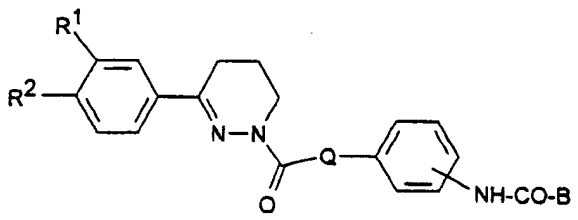
Example I: Inhalation spray

14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is

dispensed into commercially available spray vessels having a pump mechanism. The solution can be sprayed into the mouth or nose. One puff of spray (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Claim

1. Use of compounds of the formula I



I

in which

B	is A, OA, NH_2, NHA, NAA' or an aromatic heterocycle having 1 to 4 N, O and/or S atoms which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or OA,
Q	is absent or is alkylene having 1 to 6 C atoms,
R^1, R^2	each independently of one another are -OH, OR^5, $-S-R^5$, $-SO-R^5$, $-SO_2-R^5$, Hal, $-NO_2$, $-NH_2$, $-NHR^5$ or $-NR^5R^6$,
R^1 and R^2	together are also $-O-CH_2-O-$,
R^5 and R^6	each independently of one another are A, cycloalkyl having 3-7 C atoms, methylenecycloalkyl having 4-8 C atoms or alkenyl having 2-8 C atoms,
A, A'	each independently of one another are alkyl having 1 to 10 C atoms which may be substituted by 1 to 5 F and/or Cl atoms and

Hal is F, Cl, Br or I,

and/or their physiologically acceptable salts for preparing a medicament for the treatment of osteoporosis, tumours, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis and AIDS.